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## Stem cell therapy for COVID-19 and other respiratory diseases: Global trends of clinical trials

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### Abstract

Respiratory diseases, including coronavirus disease 2019 and chronic obstructive pulmonary disease (COPD), are leading causes of global fatality. There are no effective and curative treatments, but supportive care only. Cell therapy is a promising therapeutic strategy for refractory and unmanageable pulmonary illnesses, as proved by accumulating preclinical studies. Stem cells consist of totipotent, pluripotent, multipotent, and unipotent cells with the potential to differentiate into cell types requested for repair. Mesenchymal stromal cells, endothelial progenitor cells, peripheral blood stem cells, and lung progenitor cells have been applied to clinical trials. To date, the safety and feasibility of stem cell and extracellular vesicles administration have been confirmed by numerous phase I/II trials in patients with COPD, acute respiratory distress syndrome, bronchial dysplasia, idiopathic pulmonary fibrosis, pulmonary artery hypertension, and silicosis. Five routes and a series of doses have been tested for tolerance and advantages of different regimes. In this review, we systematically summarize the global trends for the cell therapy of common airway and lung diseases registered for clinical trials. The future directions for both new clinical trials and preclinical studies are discussed.

**Key words:** Pulmonary diseases; COVID-19; Cell therapy; Exosomes; Clinical trial

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**Core tip:** Preclinical studies demonstrate significant improvement of lung disorders by stem cells and extracellular vesicles. Completed clinical trials show cell-based therapies are safe and tolerant for acute and chronic respiratory diseases. Current challenges for cell therapy of pulmonary illnesses are long-term safety, efficacy, and personal

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## INTRODUCTION

Respiratory diseases are a top-ranked cause of death toll worldwide<sup>[1]</sup>. Acute and chronic lung diseases, including coronavirus disease 2019 (COVID-19)<sup>[2]</sup>, acute lung injury (ALI)/acute respiratory distress syndrome (ARDS), bronchopulmonary dysplasia (BPD), pulmonary arterial hypertension (PAH), silicosis, sarcoidosis, extensively drug-resistant tuberculosis, chronic obstructive pulmonary diseases (COPD)<sup>[3]</sup>, and idiopathic pulmonary fibrosis (IPF), have high morbidity and mortality. Amidst the list, COPD is the third leading cause of global fatality. Rapidly accumulating evidence in preclinical models suggests that cell-based therapy may be a promising therapeutic strategy for lung injury repair<sup>[4]</sup>. For example, mesenchymal stromal stem cells (MSCs) derived from the umbilical cord blood, bone marrow, adipose, placenta, and other tissues are tested by registered clinical trials. Stem cells are able to repair injured airways and lungs by modulating multiple biological processes of the immune response, alveolar fluid clearance, cell fate, and drug delivery through paracrine and autocrine mechanisms, predominantly *via* extracellular vesicles (*i.e.*, exosomes)<sup>[5-7]</sup>. However, the safety and benefits of cell therapy for the airway and lung diseases are under investigation by increasingly registered clinical trials. To analyze the trend of the clinical trials globally for the cytotrophy of pulmonary diseases, we summarized completed and ongoing trials registered to four databases from 1997 to 2020. This review will provide a brief state-of-the-science overview of the clinical studies of the respiratory diseases using various stem cells and extracellular vesicles.

## OVERVIEW

We searched four broadly recognized databases worldwide: (1) The Clinicaltrials.gov (CT, <https://clinicaltrials.gov/>); (2) The International Clinical Trials Registry Platform (ICTRP, <http://apps.who.int/trialsearch/>); (3) The European Union Clinical Trial Regulation (EUCTR, <https://www.clinicaltrialsregister.eu/>), and (4) The PubMed databases. The total hits were 329 trials composed of 96 (CT), 23 (ICTRP), 3 (EUCTR), and 21 (PubMed) in aforementioned four databases, respectively. Some trials are with a status of “withdrawn” or had a disease condition of “complications after transplantation of stem cells”. After combining the published and dual registered studies, there are 120 trials. The vast majority of these clinical trials (82%) are testing the safety of stem cells for feasibility, tolerance, and severe adverse events (54 trials for phase I, 23 for I/II, and 21 for II). Few trials (3%) are phase III (Figure 1A). The status of these trials shows (Figure 1B): “recruiting” (30%), “not yet recruiting” (26%), “unknown” (18%), “completed” (18%), and “others” (8%). The published trails (8 of 21) are listed in Table 1. The first trial was registered in 1997, and suddenly the number shoots up mainly due to COVID-19 (Figure 1C). Geologically, the trials are predominately registered by China (42%) and the USA (22%) (Figure 1D). Currently, the main purpose of the clinical trials is to test the safety of stem cell therapy except few moving to test effectiveness. A completed list and additional features of these clinical trials can be found in the Supplementary table.

## SPECTRUM OF STEM CELLS FOR RESPIRATORY DISEASES

Stem cells include multipotent embryonic stem cells and progenitor cells. MSCs are used in most clinical trials, probably based on the fact of well-tolerated and free of serious adverse events<sup>[8]</sup>. Another consideration is availability. MSCs can be easily collected from the bone marrow, adipose tissue, muscle, peripheral blood, umbilical cord blood, and placenta<sup>[9]</sup>. Umbilical cord blood derived-MSCs (UCB-MSCs) were



**Table 1** Characteristics of published clinical trials

ID	Condition	Cell type	Case	Phase	Duration	Result
NCT00683722	COPD	Progenitor cells	62	II	2 yr	No infusional toxicities, deaths, and SAE
NCT01110252	COPD/ Emphysema	BM-MSCs	4	NA	1 yr	No SAE; significant improvement in the quality of life and clinical conditions
NCT01306513	Emphysema	BM-MSCs	10	I	8 wk	No SAE; increased CD31 expression
NCT01775774	ARDS	BM-MSCs	9	I	8 wk	No infusional toxicities, no SAE
NCT02097641	ARDS	BM-MSCs	60	II	8 wk	No SAE; improve MV and PEEP
NCT00257413	PAH	EPCs	31	NA	12 wk	No SAE; increased MWD, PAP, PVR, and cardiac output
NCT00469027	PAH	EPCs	7	I	1 yr	Well tolerated; increased MWD
NCT02181712	BOS	MSC	9	I	4 wk	No SAE

COPD: Chronic obstructive pulmonary disease; ARDS: Acute respiratory distress syndrome; PAH: Pulmonary arterial hypertension; BOS: Bronchiolitis obliterans syndrome; MWD: Mean walked distance; SAE: Severe adverse events; MV: Minute ventilation; PEEP: Positive-end expiratory pressure; PAP: Pulmonary artery pressure; PVR: Pulmonary vascular resistance; NA: Not available.

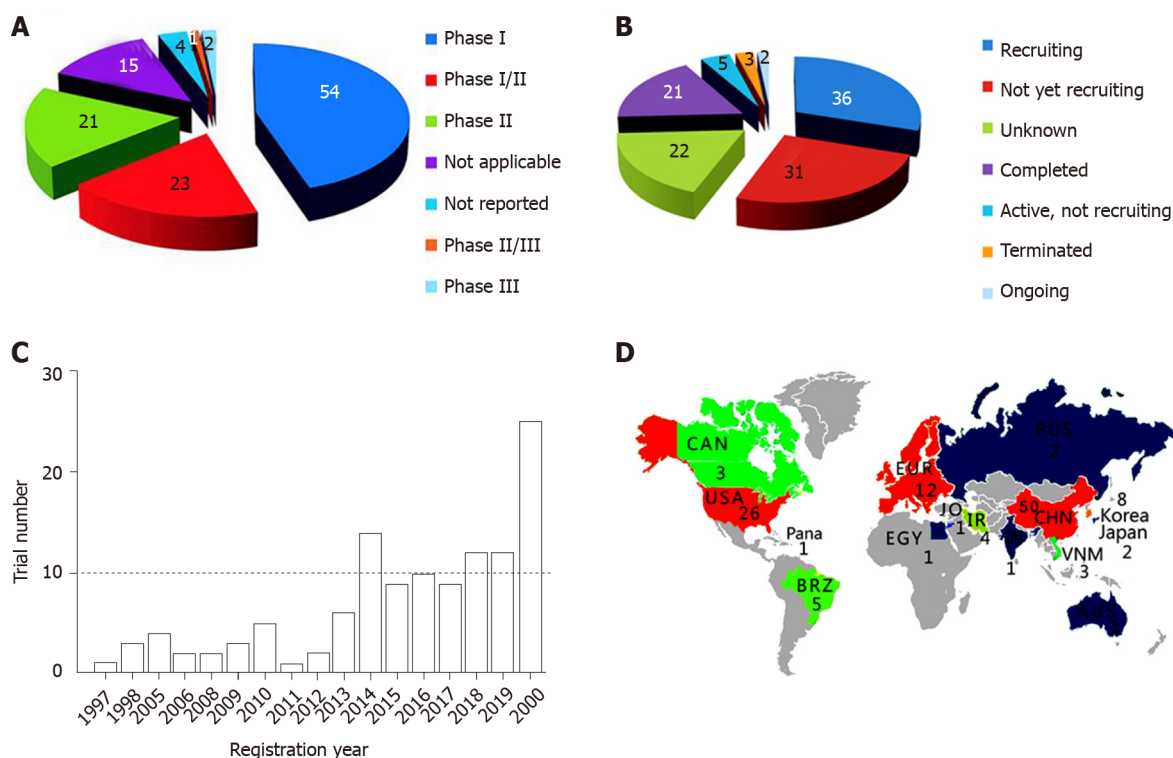
used in 43 trials, bone marrow derived-mesenchymal stromal cells (BM-MSCs) in 24 trials, mesenchymal stem cells in 15 trials, and adipose-derived stem cells (AD-SCs) for 12 trials (Figure 2A). Some trials are testing endothelial progenitor cells (EPCs), peripheral blood stem cells, placental mesenchymal stem cells, adult human stem cells, bronchi stem cells, menstrual blood-derived stem cells, bronchial basal cells, heart muscle progenitor cells, and lung stem cells. UCB-MSCs possess the highest proliferation rate, greatest anti-inflammatory ability, and lowest rate of senescence among all stem cells<sup>[10]</sup>. BM-MSCs and AD-SCs are the most popular autologous stem cells<sup>[11]</sup>. A combination of two or more types of stem cells is a standard regime for these clinical trials for lung diseases.

## EXTRACELLULAR VESICLES

Extracellular vesicles (EVs) may serve as paracrine for MSCs to rescue damaged cells<sup>[12]</sup>. MSC-derived EVs replicate 70% of the beneficial effects of MSCs and carry a variety of bioactive factors, including signal molecules and growth factors, to recipient cells<sup>[13]</sup>. MSC-derived EVs are beneficial to the recovery of lung diseases in animal models<sup>[14]</sup>. Pre-clinical studies have demonstrated that MSC-derived EVs significantly reduce lung inflammation and restore the function of injured lungs. It could be partially attributable to the improvement in macrophage phagocytosis and bacterial killing<sup>[15-17]</sup>. Subsequently, the safety and efficacy of MSC-derived EVs are being tested for both BPD and COVID-19 pneumonia. It seems safer to deliver MSC-derived EVs rather than MSCs.

## ROUTES AND DOSAGES

In general, the dosage of stem cells ranged from  $1 \times 10^6$  to  $1 \times 10^9$  cells/kg for a series of delivery, or a total dose of  $2 \times 10^6$  to  $1.2 \times 10^9$  cells. The dose of EVs is either  $2.0 \times 10^8$  nanovesicles daily for 5 d or one dose of 20 pmol phospholipid/kg body weight. Stem cells and EVs were delivered *via* five routes: Intravenous perfusion for 73 trials, intratracheal administration for 18 trials, subcutaneous injection for 3 trials, intranasal instillation for 3 trials, and pulmonary artery injection for 1 trial (Figure 2B). Intravenous delivery (61% of analyzed trials) is a systemic route for cell therapy. Stem cells could be easily trapped in the pulmonary microcirculatory system and home to injured lobes<sup>[18]</sup>. In contrast, local delivery, including intratracheal, intranasal, and pulmonary artery administration is the second most used route. Local delivery possesses the advantages of prolonging the half-time of cells, increasing the utilization efficacy, and decreasing side effects to other organs (off-target effects). It could be better for local lung injury repair, particularly for epithelial injury. Systemic delivery



**Figure 1 Characteristics of clinical trials.** A: Clinical phases; B: Status of trials; C: Chronological distribution; D: Geographical locations. CAN: Canada; BRZ: Brazil; EUR: Europe; EGY: Egypt; IR: Iran; RUS: Russia; CHN: China; VNM: Vietnam; AUS: Australia; Pana: Panama; JO: Jordan.

of stem cells and EVs is applicable to systemic lung injury, including sepsis, multiple organ failure, or patients with severe pulmonary edema. A concern of local administration of stem cells and EVs is the distribution in both lungs. Based on the location of gastric acid aspiration injury and influenza animal models caused by the delivery of viruses intratracheally or intranasally, the impaired lobes are limited. In current trials, both local and systemic routes are used to BPD, pulmonary fibrosis, COPD, and silicosis. Local delivery of liposomal drugs and perfluorocarbon nanoparticles to the location of lung cancers is more effective than the systemic route<sup>[19,20]</sup>. Therefore, the types, routes, and dosages of stem cells should be justified based on the personal conditions (precision/individual medicine)<sup>[21]</sup>.

## RESPIRATORY CONDITIONS REGISTERED BY CLINICAL TRIALS

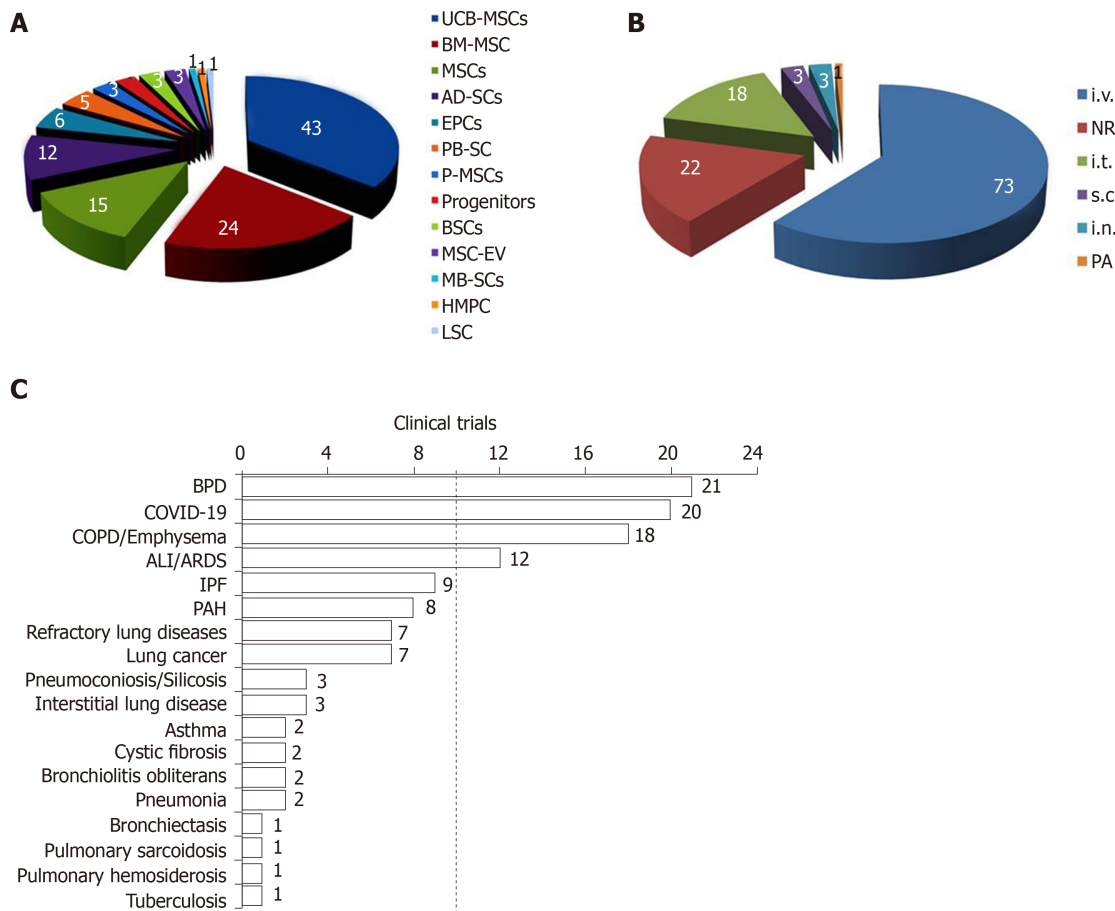
Clinical trials registered are designed to test the safety and benefits of stem cells for BPD 21 (18%), COVID-19 20 (17%), COPD/Emphysema 18 (15%), ALI/ARDS 12 (10%), pulmonary fibrosis 9 (8%), PAH 8 (7%). Few trials are for lung cancer, pneumoconiosis, silicosis, asthma, cystic fibrosis (Figure 2C). There is a significant increase since 2014 (Figure 1C), particularly after the outbreak of COVID-19.

### COVID-19

COVID-19 coronavirus started in Wuhan, China, in December 2019 and has been spreading rapidly worldwide<sup>[22]</sup>. There are no specific therapeutics yet for more than 1 million confirmed cases with 56-thousand deaths<sup>[23]</sup>. Twenty-four registered clinical trials are designed to investigate the therapeutic effects of MSCs on COVID-19 (Supplementary table). MSCs have anti-inflammatory, anti-apoptotic, antimicrobial, and anti-fibrotic properties<sup>[24,25]</sup>. COVID-19 has a higher risk of developing sepsis, multiple organ failure, including severe respiratory failure<sup>[26,27]</sup>, MSCs are assumed to have a beneficial effect for COVID-19, as supported by the promising results of a pilot study<sup>[28]</sup>. A systemic review has recently summarized the ongoing trials regarding the cell therapy of COVID-19<sup>[29]</sup>. We will, thus, not duplicate here.

### ALI/ARDS

ALI is a common vital complication of systemic and pulmonary insults and developed as ARDS in the late stages<sup>[30,31]</sup>. The fatality of ARDS is approximately 30 to 40%, and



**Figure 2 Respiratory diseases, types of stem cells, and administrative routes.** A: Type of stem cells; B: Routes of delivery; C: Respiratory diseases. COVID-19: Coronavirus disease 2019; BPD: Bronchopulmonary dysplasia; COPD: Chronic obstructive pulmonary disease; ALI/ARDS: Acute lung injury/acute respiratory distress syndrome; PF: Pulmonary fibrosis; PAH: Pulmonary arterial hypertension; UCB-MSCs: Umbilical cord blood derived-mesenchymal stem cells; BM-MSCs: Bone marrow-derived mesenchymal stem cells; AD-SCs: Adipose-derived stem cells; MSCs: Mesenchymal stem cells; EPCs: Endothelial progenitor cells; PB-SC: Peripheral blood stem cells; P-MSCs: Placental mesenchymal stem cells; MSC-EV: MSC-derived extracellular vesicles; BSCs: Bronchial stem cells; MB-SCs: Menstrual blood-derived stem cells; HMPC: Human heart muscle progenitor cells; LSCs: lung stem cells; i.v.: Intravenous; i.t.: Intratracheal; i.n.: Intranasal; PA: Pulmonary artery; s.c.: Subcutaneous; NR: Not reported.

even up to 49% in severe COVID-19 patients<sup>[27]</sup>, brings a serious economic burden globally<sup>[32-34]</sup>. MSCs are promising, as shown in preclinical models of ARDS<sup>[33]</sup>. A phase I trial has demonstrated tolerance and short-term safety (up to 6 months) of MSCs for ARDS patients<sup>[35,36]</sup>. Further, a randomized phase IIa trial of ARDS treated by allogeneic mesenchymal stromal cells confirmed the safety of MSCs in 40 patients<sup>[36]</sup>. These two completed clinical trials were registered in the United States (NCT01775774 and NCT02097641) (Table 1). In addition, the safety of MSCs for ARDS is being examined in a new phase II trial for ARDS<sup>[37]</sup>. Besides MSCs, there are 12 clinical trials registered on the International Clinical Registration and five on the Chinese Clinical Trial Registrations for testing the MSCs from diverse resources. Although the benefits of cell therapy for ARDS are uncertain, the safety may not be a concern based on the results from completed trials.

### COPD/Emphysema

COPD is characterized by tissue destruction, irreversible airflow limitation, caused by a combination of bronchitis and emphysema. COPD has high morbidity and mortality, which ranks the 3rd leading cause of deaths worldwide<sup>[38]</sup>. Common drugs for COPD are corticosteroids and bronchodilators<sup>[39]</sup>. MSCs are promising for COPD based on preclinical studies<sup>[40]</sup>. There are 18 clinical trials registered to evaluate cell therapy in COPD or emphysema totally (Figure 2). Of these, only 3 have been completed (Table 1), two phase I and one phase II demonstrated the safety of cell therapy for COPD<sup>[41-43]</sup>. Predominately, AD-MSCs and BM-MSCs are examined for COPD. Considering the limitations of small sample size and heterogeneity, a randomized, double-blind, placebo-controlled clinical trial is carried out in patients with COPD to follow up 2 years after MSCs infusion. Importantly, a phase I/II clinical study showed that four doses of UC-MSC treatment considerably alleviated the



severity of symptoms of COPD<sup>[44]</sup>. Further studies are needed to confirm the effectiveness of MSCs, optimize the sources of MSCs, and select the best route to administer MSCs.

### **BPD**

BPD is a chronic lung disease in premature infants, and usually causes various lifelong pulmonary complications (COPD and asthma)<sup>[45,46]</sup>. The current treatment strategies of the BPD are unsatisfactory. The safety and efficacy of MSCs for earlier preclinical and clinical studies have been evaluated for BPD<sup>[47,48]</sup>. Totally, 21 clinical trials are registered for cell therapy of BPD globally: China (8), Korea (7), United States (2), Spain (2), Canada (1), and Vietnam (1). Intratracheal infusion of allogeneic UCB-MSCs in preterm infants is safe and feasible<sup>[49]</sup>. Inflammatory markers and growth factors in tracheal aspirate samples decrease after MSC transplantation<sup>[50]</sup>. The same investigators have warranted a phase II clinical trial for intratracheal transplantation of UCB-MSCs to preterm infants with BPD (NCT01632475). The most of source of MSCs (90%) is UCB-MSCs in the 21 clinical trials, probably for UCB-MSCs are considered a better available source of MSCs than others<sup>[51]</sup>. Given the small sample size of these trials, the interpretations of the safety shall be cautious, and it may be too earlier to draw conclusions for the benefits of cell therapy for BPD.

### **PAH**

PAH is a progressive chronic disorder with high mortality and increasing prevalence, characterized by the remodeling of the pulmonary arteries and increased pulmonary infiltrates<sup>[52]</sup>. Interventions with specific targets for PAH have been developed<sup>[53]</sup>; however, the fatality is not reduced. Animal studies show that cell therapy may be the most potent approach for PAH<sup>[54]</sup>. Therefore, 8 trials have been registered to date (Figure 2C). Amidst, 2 have been completed<sup>[55,56]</sup>. EPCs are used in 8 clinical trials. Intravenous administration of autologous EPCs with or without gene editing of endothelial NO-synthase (eNOS) seems to be feasible and safe<sup>[55,57]</sup>. A phase II trial of *eNOS* gene enhanced EPCs for PAH is ongoing (NCT03001414). Besides, the safety and effects of AD-MSCs on PAH is being tested. Due to the phase I/II trials are not a double-blind, placebo-controlled, the efficacy of EPCs for PAH is unknown. Taken together, the use of EPCs for formal clinical treatment requires a more rigorous review and experiment.

### **IPF**

IPF is a chronic and irreversible interstitial lung disease characterized by diffuse alveolar inflammation and extracellular matrix remodeling<sup>[58]</sup>. There are no effective regimes yet, but the administration of MSCs is evaluated as a new therapy<sup>[59]</sup>. MSCs can prevent the progression of IPF in animal models<sup>[60]</sup>. In this way, there are 9 registered clinical trials based on the benefits of cell therapy in preclinical studies. In a completed trail, a single dose of 2, 10, or 20 × 10<sup>7</sup> cells/kg allogeneic BM-MSCs was intravenously delivered into 9 patients, whereas AD-MSCs were used. All three trails show the safety and well-tolerated of cell therapy and improved quality-of-life of IPF patients by MSCs<sup>[61-63]</sup>. Of note, a standardized protocol is available for clinicians<sup>[64]</sup>. Additional types of MSCs are tested in China, Australia, and Greece, including placental-derived MSCs and bronchial stem cells to compare the efficacy of them<sup>[64,65]</sup>. Given that no severe adverse effects were observed during a period of 6-month follow-up, the safety and efficacy of intravenous infusion of autologous lung spheroid stem cells are recruiting patients.

### **Others**

In addition to the aforementioned pulmonary diseases, clinical trials are registered for testing the safety and efficacy of stem cells for other refractory lung diseases, including lung cancer, silicosis, asthma, bronchiolitis obliterans, and tuberculosis (Figure 2C). Two clinical trials are recruiting bronchiolitis obliterans patients to evaluate the safety and feasibility of MSCs infusions. One phase I trial is evaluating the safety of allogeneic BM-MSCs (2-10 × 10<sup>7</sup> cells/kg, i.v.) for asthma. The safety of intranasal delivery of MSC-trophic factor for asthma (NCT02192736) has initiated too. Autologous BM-MCs is further tested for silicosis (NCT01239862) based on a previous study<sup>[66]</sup>. Radiation-induced lung injury is a new target of MSCs in the near future<sup>[67]</sup>.

## **CONCLUSION**

In conclusion, there is a rapid pace of clinical trials on stem cell therapy for lung diseases in the last 5 years. Because of the heterogeneity of pulmonary diseases, a broad spectrum of stem/progenitor cells has chosen by registered trials. Meanwhile,

diverse routes for delivering and doses have applied based on both preclinical and clinical studies. It is a long-lasting debate if MSCs result in aggregating or clumping in the injured microcirculation and carry the risk of mutagenicity and oncogenicity. EVs could at least partially resolve these concerns. Mechanistically, the restoration of stem cell niches could be an innovative mechanism for cell therapy<sup>[68,69]</sup>. To date, most of these trials are at an early stage for evaluating safety, feasibility, tolerance, and potential efficacy. Few clinical studies have described clinical improvements. Therefore, further optimization for cell therapy on respiratory diseases needs to be explored by more phase III and IV clinical trials. Cell therapy has significant challenges for gene editing stem cells, optimized route and dose, intervention regimes and applications for individual case, nevertheless, cell-therapy offers a most innovative strategy for unmanageable respiratory diseases.

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